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Implementation Example 1 (Patent p. 5, last lines)

D-Phenylalanine (24.36 g) was dissolved in water (155 g) and an aqueous 10 wt % solution of KOH (93.9 g), and acetone (70.4 g) added. trans-4-Isopropylcyclohexyl-carbonyl chloride (22.77 g) was added to this solution during 1.5 hours. In order to maintain the pH at 13.7 - 14.3 during this time, aqueous 10 wt % solution of KOH (71.8 g) was added; furthermore, cooling was applied while keeping the temperature below 15°C and a nateglinide containing acylation reaction mixture of 438.2 g was obtained.

In order to regulate the concentration, a portion (202.5 g) of the acylation reaction mixture was treated with water (12.6 ml) and acetone (11.0 g), after which a mixture of 35 wt % aqueous HCl (12.0 g) and water (60.2 g) was added during 1.5 hours. When the crystallisation slurry obtained (acetone concentration 14.6 wt %) was stirred overnight at 66°C the slurry had settled out, stirring was discontinued and the deposited crystals separated. When viewed under the microscope the state of the crystals was that of bundles of needle-like crystals. The average size of these aggregates, was about 0.2 mm width and 2.0 mm length. When examined by powder X-ray, the presence of diffraction peaks at 8.1°, 13.1°, 19.6°, 19.9° (2θ) was confirmed, which confirmed the presence of the H-form.

Comparative Example 1

An acylation mixture as in Implementation Example 1, with 8 wt % acetone, was stirred overnight at 45°C. The slurry obtained did not tend to precipitate. Under the microscope there were bundles of needles but compared to the crystals obtained in Implementation Example 1 the individual needles were small with a low degree of bundling. Their size was about 0.02 mm in width and 0.1 mm in length.

Comparative Example 2

An acylation mixture as in Implementation Example 1, with 22 wt % acetone, was stirred overnight at 73°C. but it oiled and failed to crystallise.

Implementation Examples 2 to 10 and Comparative Examples 3 to 12  
(Patent p. 7)

In the experiments below the same reaction and crystallisation operations as in Implementation Example 1 were carried out, with modification of the acetone concentration and temperature of crystallisation. For each slurry as obtained in Implementation Examples 2 to 10 and Comparative Examples 3 to 12 the state of precipitation is observed and the crystals obtained are observed under a microscope.

Implementation Example 11

(Separation rating 1: acetone concentration 14%, crystallisation temperature 65°C)  
In a 2KL capacity reaction-crystallisation vessel, the acylation reaction is carried out using D-phenylalanine (38.14 kg) and trans-4-isopropylcyclohexylcarbonyl chloride

(40.1 kg), and, in amounts corresponding to the proportions in Implementation Example 1, water, 10% KOH and acetone. An acylation mixture (728 kg) containing nateglinide is obtained. This reaction mixture is added to a mixture of water (249 L) and aqueous 35 wt % HCl, and acetone (62 L) then added, adjusting the total acetone concentration to 14.4 wt %. After 17 hours' stirring at 63 - 65°C, the mixture was cooled to 30°C. When the slurry obtained was examined under the microscope needle-like crystals in a state of cohesion were observed. The whole slurry (1200 L) was divided into three batches of roughly 400 L, for each of which the solid was separated from the liquid in a 36" diameter basket centrifuge. After the solid-liquid separation, the solids in the centrifuge were each washed with water (150 ? BS-from CE 13 below: Liters). (The time) from addition of the rinse liquid until there was no more filtrate was about 16 minutes. The weight of total moist solid obtained from separation in three batches was 104.9 kg, and the average loss in weight after drying at 105°C for 2 hours was 35.9%.

#### Comparative Example 13

(Separation rating 2: acetone concentration 8%, crystallisation temperature 45°C)

With the same equipment as in Implementation Example 11 and carrying out the acylation reaction on the same scale of D-phenylalanine, the nateglinide containing slurry was obtained (727 kg). This was regulated to an acetone content of 8 wt %, heated at 45°C and stirred for 17 hours when it was cooled to 30°C.

When the slurry was examined under the microscope there was almost no cohesion.

The whole slurry (1200 L) was divided into four batches of roughly 300 L, each of which was centrifuged to separate the solid from the liquid. the crystals from each separation were washed with water (110 L). From addition of the rinse liquid until there was no more filtrate required an average of about 30 minutes.

The weight of total moist crystals obtained from the separation in ~~three~~ batches was 162.3 kg, and the average loss in weight of these crystals after drying was 60.8 %.

The results of Implementation Examples 2 to 11 and Comparative Examples 3 to 13 are collected and shown in Table 1.

Table 1

|       | Acetone conc.<br>(wt %) | Crystallisn. Temp<br>(°C) | Precipitation | Microscopic Observation |
|-------|-------------------------|---------------------------|---------------|-------------------------|
| CE 3  | 8                       | 45                        | 0             | like CE 1               |
| CE 4  | 8                       | 55                        | 0             | like CE 1               |
| IE 2  | 10                      | 70                        | +             | like IE 1               |
| CE 5  | 11.5                    | 57                        | 0             | like CE 1               |
| IE 3  | 12                      | 65                        | +             | like IE 1               |
| IE 4  | 12                      | 70                        | +             | like IE 1               |
| CE 6  | 13                      | 55                        | 0             | like CE 1               |
| IE 5  | 13                      | 60                        | +             | like IE 1               |
| CE 7  | 13.5                    | 73                        | oiling        | oiling                  |
| CE 8  | 14                      | 50                        | 0             | like CE 1               |
| IE 6  | 14                      | 72                        | +             | like IE 1               |
| CE 9  | 14.5                    | 73                        | oiling        | oiling                  |
| CE 10 | 14.5                    | 78                        | oiling        | oiling                  |
| IE 7  | 14.6                    | 66                        | +             | like IE 1               |
| IE 8  | 15                      | 60                        | +             | like IE 1               |
| IE 9  | 16                      | 65                        | +             | like IE 1               |
| IE 10 | 16                      | 67                        | +             | like IE 1               |
| CE 11 | 20                      | 50                        | 0             | like CE 1               |
| IE 11 | 20                      | 58                        | +             | like IE 1               |
| CE 12 | 22                      | 65                        | oiling        | oiling                  |
| CE 13 | 22                      | 73                        | oiling        | oiling                  |

(BS: IE = Implementation Example; CE = Comparative Example;  
+ = there is precipitation; 0 = there is no precipitation)

It is clear from the results of the above Implementation and Comparative Examples that by crystallizing out the crystals using the precipitation conditions (described) in the manufacturing method of this Invention, filterable satisfactory crystals are formed. In an industrial scale preparation also, it becomes possible to isolate nateglinide crystals efficiently from the reaction mixture.

Claims

(Patent p. 10, Adobe p. 11)

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Scope of the Claims

1. A process for producing nateglinide crystals which comprises reacting trans-4 isopropylcyclohexylcarbonyl chloride with D-phenylalanine in a mixed solvent consisting of a ketone solvent and water in the presence of alkali to obtain a reaction mixture containing nateglinide, adding an acid to the reaction mixture to acidify it and regulating the temperature to 58 - 72°C and the concentration of the solvent ketone to more than 8% and less than 22% for crystallisation to occur.
2. A process according to Claim 1 above where the regulation of the ketone solvent concentration is carried out by adding the above-mentioned ketone solvent to the above-mentioned reaction mixture.
3. A process according to Claim 1 above where regulation of the above-mentioned ketone solvent concentration is regulated by adding acetone to the acylation reaction mixture.
4. A process according to Claim 1 above where, the above-mentioned ketone solvent in general being acetone, the acetone concentration in the reaction mixture at the time of the above-mentioned crystallisation is 12 - 16 wt %.
5. A process according to Claim 1 above where the above-mentioned crystals are H-form crystals.
6. A process for producing nateglinide H-form crystals which comprises reacting trans-4 isopropylcyclohexylcarbonyl chloride with D-phenylalanine in a mixed solvent of acetone and water in the presence of alkali to obtain a reaction mixture containing nateglinide, adding an acid to the reaction mixture to acidify it and regulating the temperature to 58 - 72°C and the concentration of the solvent ketone to more than 8% and less than 22% and crystallising.
7. A process according to Claim 6 above where the regulation of the above-mentioned acetone concentration is carried out by adding acetone to the above-mentioned acylation reaction mixture.
8. A process according to Claim 6 above where, during the above-mentioned separation of the crystals, the acetone concentration is 12-16 wt %.
9. Nateglinide crystals obtained by the method described in Claim 1.
10. The crystals recorded in Claim 9 in which these crystals have an average major axis of over 1 mm and an average minor axis of over 0.1 mm.

11. The crystals recorded in Claim 9 where the above-mentioned crystals are H-form.
12. Nateglinide H-form crystals as obtained by the method recorded in Claim 6.
13. H-Form crystals as recorded in Claim 12 in which these crystals have an average major axis of over 1 mm and an average minor axis of over 0.1 mm.